Remarks

Before addressing the pending rejections it is helpful to revisit the nature of the claimed invention and the procedural history of this case as each is relevant to the issues at hand.

I. Procedural History

On December 30, **1994**, Applicants filed the specification of the instant application -- Serial No. 366,651 ("the '651 application"). The '651 application was subject to a restriction requirement including seven different methods of use. Applicants elected Group I, directed to the treatment of a specific disorder, allergic rhinitis, in a specific patent population, humans, using a specific compound -- descarboethoxyloratadine ("DCL"). After prosecution on the merits, this method of use issued as U.S. Patent No. 5,595,997. A divisional, Serial No. 783,393, was filed on January 13, 1997 directed to the specific use of DCL in treating another disorder -- allergic asthma. Such claims issued in U.S. Patent No. 5,731,319.

The instant application was filed as another divisional on November 23, 1999, directed to the specific use of treating urticaria with the specific compound DCL in a specific patient population humans.[1]

The Examiner has rejected such use claims under § 103 as obvious in view of the patent to the compound -- DCL -- Villani U.S. 4,659,716 ("Villani"), and the Merck Manual's discussion of the disease urticaria. This very rejection was the subject of an Appeal which Applicants briefed before the Board of Patent Appeals and Interferences on **November 8, 2001**. In lieu of the Examiner's Answer, some two and one-half **years** later, the Examiner reopened *ex parte* prosecution by rejecting the claims again under 35 U.S.C. § 103 for the same reasons using the same references. The Examiner admitted in informal telephone interviews and in the personal interview that the case of obviousness was poor and that the case was pulled from appeal to avoid a reversal by the Board.

Despite this admission, which is of tremendous concern to Applicants in this matter, Applicants put forth additional evidence to rebut the Examiner's contention and to support the patentability of the claim under § 103 over the cited references

[1] The claims have also been amended to include specific doses and routes of administration or both.

since they were again in *ex parte* prosecution. Further, Applicants amended claims to narrow issues. Even though the evidence of non-obviousness mounts, the Examiner maintains the very same legally improper § 103 rejections.

On December 13, 2005 a personal interview was held with the Examiner and his Supervisor in the hope that the evidence of record would be properly considered and weighed under controlling law.

The Applicants' record of the substance of the interview follows below after the summary of the invention.

II. The Claimed Invention

It is undisputed that the claimed invention -- the treatment of urticaria in humans using a specific amount (5 mg or less) of a specific compound (DCL) in a specific patent population (humans) -- is novel.[2] This new use of a known compound is also nonobvious. Indeed, the Patent Office has cited no reference dated before Applicants' December 1994 filing date that suggests all of the limitations of the claims.

There is overwhelming evidence of nonobviousness in the current record, including references that teach away from the cited references, unexpected results, and expert declarations that opine the invention was not obvious.

Applicants request that the claims be reconsidered, the evidence properly weighed and the claims allowed. Alternatively, an expedited appeal is warranted given the PTO's procedural delay.

III. Applicants' Statement of the Substance of Interview and Response to the Examiner's Interview Summary of Record

A personal interview with Supervisory Patent Examiner Jiang and Patent Examiner Crane, as well as with Messrs. Barker, Insogna and Choi, attorneys for Applicants, was held on December 13, 2005.

During the interview, the Examiners and Applicants discussed the § 103 rejections that have been pending for some time in this application. In addition, Applicants briefly discussed the claims and pending rejections in related co-pending

[2] Indeed, the claims are novel without the dose limitations or the route of administration limitations currently in the claims.

application no. 09/039,260. After setting forth why the cited references did not present a *prima facie* case of obviousness, Applicants respectfully pointed out that the evidence of record, in particular, the Storms Declaration was improperly ignored. Applicants emphasized that in the context of an obviousness rejection under 35 U.S.C. § 103, all relevant art must be considered, citing *Graham v. John Deere Co.*, 381 U.S. 1 (1966) and *In re Kuderna*, 426 F.2d 385, 389 (C.C.P.A. 1970), whether such evidence relates to the toxicity/safety or potency/efficacy of a drug or method. Indeed, safety issues concerning the adverse side effects of a drug are routinely considered by the PTO and the courts in assessing obviousness. (*See In re May*, 574 F.2d 1082, 1092-3 (C.C.P.A. 1978); *Ex parte Barberich et al.*, Appeal No. 2005-0906 (July 12, 2005), attached hereto as **Exhibit 1**, at pages 10-11).

Examiner Crane stated, citing *Ex parte Balzarini*, 21 U.S.P.Q.2d 1892 (B.P.A.I., 1991), that safety issues are pertinent only to the FDA, and cannot be considered in assessing patentability.[3] While Applicants agreed that the Board and the courts have repeatedly reminded the PTO that it is not the FDA, such admonitions were made in the context of §§ 101 and 112. (*See In re Brana*, 51 F.3d 1560, 1567-1568 (Fed. Cir. 1993); *see also Balzarini*, 21 U.S.P.Q.2d at 1897). For example, in the case cited by Examiner Crane, the issue addressed was whether human clinical data is required to prove utility under 35 U.S.C. §§ 101/112,[4] such law is not applicable to the § 103 issues at hand.

Applicants repeatedly stated during the interview that all relevant prior art, whether it relates to toxicity or potency, would have been considered by one of ordinary skill at the time of the claimed invention and must be considered by the Examiner in connection with the determination of (non)obviousness under § 103. (*See, e.g., Manual of Patent Examining Procedure* ("MPEP") § 716.01 (a)). Applicants provided the Examiners two cases in this regard, *In re Zenits*, 333 F.2d 924 (C.C.P.A. 1964) and *Ex parte Sasajima*, 212 U.S.P.Q. 103 (B.P.A.I. 1980), each of which is discussed below.

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[3] This erroneous legal proposition is replete in the final office action.

[4] Even in the §§ 101/112 context, the Board held that clinical data is not required, but certainly did not hold that such data cannot be considered. (*See Balzarini*, 21 U.S.P.Q.2d at 1897).

For example, Applicants invited the Examiners' attention to several references that ***teach away*** from the claimed invention (namely Michele, Parslew, McClintok and Knowles, each of which is discussed below), and pointed out that proper consideration had not been given to these references. Examiner Crane again indicated, in connection with such references and also with Storms Declaration, that such evidence is irrelevant, based on his contention that those of ordinary skill in the art are "experimentalists" and not clinicians or physicians. Applicants pointed out that since the claims recite "method of treatment," those of ordinary skill in the art include physicians and clinicians that treat urtacaria. Applicants also pointed out that Villani, the primary reference cited by the Examiner, specifically refers to "clinicians" as relevant artisans at, for example, column 11, lines 24-28. Nevertheless, Examiner Crane persisted that the art that teaches away and the Storms Declaration were irrelevant to the PTO's assessment of obviousness.

In addition, Applicants suggested certain claim amendments which, they believe, would further remove the pending claims from the disclosure of Villani and the other cited references. Such amendments are reflected in the claims presented herein.

In what appeared to be an effort to side step the improper § 103 rejections, Examiner Jiang brought up the possibility of a new rejection of inherent anticipation in view of the prior art knowledge of the use of loratadine, the parent of the compound recited by the pending claims.[5] Applicants pointed out that a substantially similar rejection was reversed by the Board in connection with assignee's application no. 09/527,844. (*See Ex parte Barberich,* **Exhibit 1**). The decision from the Board is discussed below in more detail.

Finally, Applicants addressed the Examiner's contention that the unexpected results found in the specification were not statistically significant. In particular, Applicants offered a Declaration of Dr. Paul M. Tarantino, Jr. ("Tarantino Declaration," which is being filed herewith) that rebutted the Examiner's contention as to the meaning of the data disclosed in Example 4 of the instant application to one of ordinary skill.

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[5] A brief discussion of *Schering Corp. v. Geneva Pharmaceuticals, Inc.*, 339 F.3d 1373 (Fed. Cir. 2003) took place.

In sum, no agreement was reached. Applicants noted that they would present additional evidence, make the amendments discussed to narrow the claims and would submit an amendment after final, along with the Tarantino Declaration.

IV. Amendments

Claims 34 and 39-40 are pending in this application. Claims 36, 38 and 50 are canceled in this amendment without prejudice to Applicants' rights to pursue the subject matter recited by them in one or more divisional, continuation, and/or continuation-in-part applications.

Based upon the discussion at the personal interview, claim 34 is amended to recite, in part, the oral administration of a specific amount of DCL. Support is found, for example, on page 14, lines 15-16 and page 15, lines 6-7 of the specification.

Thus, as amended, the claims recite a method of treating a specific disease urticaria in a human using a specific amount of a specific compound. Neither the disease nor the amount is suggested by the cited art, as discussed below.

V. Miscellaneous Matters

As requested by the Examiner, copies of E-9, E-10 and E-11 from the Storms Declaration are resubmitted herewith, and their bibliographic information is listed in the "List of References Cited by Applicant," enclosed herein. Execution of this document to evidence consideration of the references is respectfully requested. Since Applicants were not able to obtain the bibliographic information of E-6, E-6 is again included without such information. Consideration of this document is still requested.

VI. Argument and Response to Rejections

Applicants respectfully submit that all of the pending claims are patentable under 35 U.S.C. § 103 over the cited art for the following reasons.

A. The Rejection Under 35 U.S.C. § 103(a), over Berkow and Villani, Should Be Withdrawn

On pages 2-6 of the Office Action, claims 34, 36, 38-40, and 50 are rejected as allegedly obvious over Berkow *et al.*, *The Merck Manual of Diagnosis and Therapy*, 16th Ed., pp 332-334 (1992) ("Berkow") in view of U.S. Patent No. 4,659,716 to Villani *et al.* ("Villani"). In particular, it is alleged that Berkow discloses that

symptoms of urticaria can be relieved with an antihistamine, and Villani discloses DCL and related compounds are antihistamines, thus the claims are obvious. Applicants respectfully traverse this rejection. As shown below, the Examiner is not properly considering all the relevant art or the full teachings of the art. In fact, the Examiner is ignoring disclosures that contradict his rejection.

Berkow merely discloses that symptoms of urticaria usually can be relieved by certain antihistamines. Specifically, Berkow only provides example of three first-generation antihistamines that may be used to treat urticaria.[6] Thus, Berkow does not and cannot render the claims to the use of a specific second-generation non-sedating antihistamine -- DCL -- obvious. Since Berkow is silent as to DCL, it also cannot be fairly said to suggest anything about the use of a specific amount of DCL to that urticaria. In sum, Berkow does not provide any motivation or suggestion to those of ordinary skill in the art to even try second generation antihistamines against urticaria, much less suggest the use of DCL at the claimed doses.

The Examiner contends that the claims are obvious because, although Applicants "allege[s] that the Berkow reference fails because it must teach the specific active ingredient specified by the instant claims," such allegation is "the standard for anticipation, not the obviousness." (Office Action, page 4). However, Applicants never stated that Berkow must be an anticipatory reference. Instead, Applicants pointed out that the claims are not obvious because Berkow alone or in combination with Villani makes no suggestion to even try the claimed invention, much less provide a reasonable expectation of success as is required by law. (*See, e.g., In re Dow Chemical*, 837 F.2d 469, 473 (Fed. Cir. 1988)). Moreover, Applicants repeatedly argued that there is no suggestion to use DCL or motivation to select and use DCL, in Berkow alone or in combination with Villani, as is required by law.[7] (*See, e.g., WMS Gaming Inc. v. International Game Technology*, 184 F.3d 1339, 1355, 51 U.S.P.Q.2d 1385, 1397 (Fed. Cir. 1999)).

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[6] First-generation antihistamines which are known to cause sedation differ from second-generation antihistamines in structure and activity. (*See, e.g., Goodman & Gilman's Pharmacological Basis of Therapeutics*, 9th Ed., page 589, Table 25-1 (1996)).

[7] Why this deficiency, *e.g.*, no motivation, is not cured by Villani is discussed below. In other words, Applicants' submission is not based on their analysis of Berkow alone, as the Examiner appears to suggest. (*See*, Office Action, page 4). Further, as discussed below, whether Villani or Berkow is the primary reference is irrelevant as in either case the combination does not render the invention obvious.

Berkow, by disclosing oral antihistamines *usually* are effective in treating the symptoms of urticaria, suggests that not all antihistamines are effective in treating urticaria (a point which the Examiner acknowledges). With this fact in the record, Berkow alone or in combination with Villani cannot provide any specific suggestion or motivation for those of ordinary skill in the art to use DCL for the treatment of urticaria. (*See* Applicants' Response of May 18, 2005, page 6 and Office Action, page 3). This is especially true because all of the examples provided in Berkow are first generation antihistamines which exhibit a tranquilizing effect while DCL is a non-sedating second generation antihistamine.

Further, Berkow and Villani must be read in light of references that teach away from the use of antihistamines for the treatment of urticaria. In this regard, Applicants respectfully invite the Examiner's attention to the Board's decision (**Exhibit 1**) in connection with U.S. application no. 09/527,844 ("the '844 application"). In '844 application, the claims at issue recited, in part, a method of treating a disorder by administering a ziprasidone metabolite. (**Exhibit 1**, page 1). The Board held, based on certain portions of a cited reference that teach away from the claimed invention, that the claims were not obvious.[8] (*Id.*, page 10). In reaching this conclusion, the Board confirmed that "[o]bviousness is determined in view of the sum of all of the relevant teachings in the art, not isolated teachings in the art." (*Id.*, page 11, citing *In re Kuderna*, 426 F.2d at 389 and *In re Shuman*, 361 F.2d 1008, 1012 (C.C.P.A. 1966)). The Board also confirmed that "[i]n assessing the teachings of the prior art references, the examiner should also consider those disclosures that may teach away from the invention." (*Id.*, citing *In re Geisler*, 116 F.3d 1465, 1469 (Fed. Cir. 1997)).

Applicants respectfully point out that there is abundance of evidence in the record that provides information contradictory to the Examiner's reading of Berkow. For example, Michel *et al.*, *Contact Dermatitis*, 36: 147-149 (1997), attached hereto as **Exhibit 2**, teaches that even the gold standard for urticaria and one referred by Berkow (hydroxyzine) can cause urticaria. (*See also*, Parslew *et al.*, *Clin. Exp. Allergy*, 30: 1161-1165 (2000), attached hereto as **Exhibit 3**, teaching that certain

[8] As discussed above, the Board first held that the claims directed to method of treatment using a metabolite of a known compound are not anticipated by the prior art disclosure of the parent compound or its use and metabolism. (*See* **Exhibit 1**, pages 5-8).

types of urticaria do not respond to antihistamines; and McClintock, *The New Zealand Medical Journal*, 108: 208 (1995), attached hereto as **Exhibit 4**, teaching that terfenadine, another second-generation antihistamine, can cause skin reactions). Thus, the Examiner's allegation that Berkow suggests that all antihistamines are effective in treating urticaria, even assuming it is true, is clearly contradicted by these references. When these teachings are properly considered by the Examiner, it is clear that the rejection of the claims over Berkow must be withdrawn. (*See, e.g., W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984)).

In addition, the claims as amended are now further removed from the disclosure of the cited art as they require a specific dose of the compound recited. Again, even if Berkow and Villani when combined can be said to suggest the use of DCL for urticaria, they do not suggest the low amounts recited by the claims, much less provide the legally reasonable expectation of success. (*Dow Chemical*, 837 F.2d at 473).

Villani (whether a primary or secondary reference) does not render the claimed invention obvious (or remedy the deficiencies of Berkow) because it also provides no motivation to use DCL for the treatment of urticaria, much less motivation to use the specific amount of DCL in the method as claimed. In this regard, Applicants point out that:

1) Villani, by providing only an assay purportedly indicating the antihistaminic effect of DCL, does not provide any evidence of DCL's usefulness in a method for the treatment of urticaria (*See* Storms Declaration, ¶ 6-9);

2) Villani motivates the ordinary skilled clinician to use amounts greater than 5 mg per day to treat allergic conditions (Villani, column 11, lines 24-33); thus, in Applicants' view, Villani does not suggest the lower amounts recited by the pending claims (*See also* Example A and B of Villani that teach oral compositions of 100 mg and 500 mg, **20 to 100** times over that claimed by the instant application); and

3) Those of ordinary skill in the art, at the time of this invention, would have been discouraged from using DCL for any allergic treatment,

especially urticaria, due to concerns that the adverse effects associated with structurally similar compounds, including cardiac side effects and potential for promotion of tumor growth, would be shared by DCL. (*See* Yap *et al.*, *Clin. Exp. Allergy*, 29(supp.1): 15-24 (1999) and *Goodman & Gilman's Pharmacological Basis of Therapeutics*, 9th Ed., 1607 (1996), attached hereto as **Exhibits 5** and **6**, respectively; *see also* Storms Declaration, ¶ 12-17).

The Examiner disregards all the pertinent evidence of non-obviousness (or lack of motivation)[9] by contending that the Storms Declaration is relevant to FDA standards, but not to the patentability of the pending claims. (*See* Office Action, pages 4-5). In particular, the Examiner concludes that "patentability, except where there is clear evidence of inoperability, is entirely different determination" than FDA proceedings. (*Id.*, page 4). Applicants respectfully point out that the Storms Declaration was submitted to show that those of ordinary skill in the art would not have been motivated to even try DCL for the treatment of urticaria in view of the toxicity concerns associated with structurally similar second-generation antihistamines. Such evidence of skilled artisans is routinely considered by the USPTO and the courts (*In re May*, 574 F.2d at 1092-3; *Ex parte Barberich*, **Exhibit 1**, pages 10-11), notwithstanding the fact that human clinical trial assessment is the purview of the FDA and not a requirement for patentable utility under 35 U.S.C. §§ 101/112. (*See In re Brana*, 51 F.3d at 1567-1568).

Indeed, the Examiner's complete disregard of the evidence, provided in the Declaration and related articles, is flatly contrary to well-established legal principles. It is well-settled that, "affidavits or declarations, when timely presented, containing evidence of criticality or unexpected results, ... must be considered by the examiner in determining the issue of obviousness of claims under 35 U.S.C. § 103." (*MPEP* § 716.01 (a) (emphasis added) (citing *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1538 (Fed. Cir. 1983)). Furthermore, the law is clear on that side effects or toxicities of a chemical compound, provided in an affidavit or a declaration, must be considered by the examiner in assessing the (non)obviousness. (*See, e.g., In re Zenitz*, 333 F.2d at 928, attached hereto as **Exhibit 7** (holding that a compound's lower

[9] This is legally improper, as discussed herein.

undesirable side effects, disclosed in an affidavit, "must be considered in determining the patentability of the claimed compound"); *see also*, *In re Sasajima*, 212 U.S.P.Q. at 105, attached hereto as **Exhibit 8** (holding that a claimed compound's low toxicity "must be considered in determining the patentability of the ... claims."); *see also In re May*, 547 F.2d at 1092-3 (increased potency with decreased addictiveness has sufficient unexpected results to rebut a *prima facie* case of obviousness)). Therefore, Applicants respectfully point out that the Examiner's disregard of the Storms Declaration and the reference cited therein, as allegedly being pertinent only to FDA standards, is legally improper.

Further, to the extent that the Examiner contends that toxicity or safety concerns are only relevant to clinicians and not "experimentalists,"[10] Applicants point out that Villani refers to "clinicians" at column 11 when suggesting doses above 5 mg per day for oral administration to treat "conditions." Thus, Dr. Storms' opinion as a clinician is relevant and must be properly considered. Indeed, as the claimed invention is directed to a medical treatment method, the ordinary skilled artisan clearly includes clinicians.

Significantly, Applicants point out that in referring to Compound B, the 8-fluoro analogue of DCL, Villani points to this compound as beneficial to its "very low toxicity." Again, the reference relied upon by the Examiner refers to the very type of data that Examiner wishes to ignore -- toxicity data! What more can be shown to prove the relevance of what the Examiner blithely ignores?

Moreover, the Examiner repeatedly alleges that the Storms Declaration "does not provide an adequate factual basis for disqualification of" Berkow and Villani because the declaration "has not provided an adequate basis to support the conclusion that [Berkow and Villani] are inoperative." (Office Action, page 4 and 5). Again, the Examiner appears to misconstrue Applicants' argument.[11] The Storms Declaration and the references cited therein <u>are</u> relevant to the assessment of whether those of ordinary skill in the art would have been motivated to try to use DCL for the treatment

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[10] Applicants fail to appreciate the Examiner's repeated reference to "experimentalists" since such has never been defined.

[11] Applicants point out that one of the standards for (non)obviousness is whether the cited references would have <u>motivated</u> those of ordinary skill in the art, <u>not</u> whether the cited references are operable or not. (*See WMS Gaming Inc.*, *supra*). The Storms Declaration provides evidence as to <u>the lack of motivation</u>. (*See* Storms Declaration, ¶ 12-17).

of urticaria and whether they would have had a reasonable expectation of success. (*See Dow Chemical, supra*).

In this regard, those of ordinary skill in the art would not have been so motivated because they would have been concerned about the potential for toxicity in using DCL since compounds that share structural similarities with DCL (*e.g.*, loratadine and astemizole) when used in treating disease were known to be associated with various adverse effects, some of which are very serious. (*See* Good *et al.*, *Journal of Cardiology*, 74(15): 207 (1994) and Nyman *et al.*, *Lakartidningen*, 99(25): 2281 (1992), submitted as Exhibits E5 and E7 to Storms Declaration; *see also* Yap and Goodman (**Exhibits 5** and **6**) and Storms Declaration, ¶ 12-17). Considering that urticaria is not a life-threatening disorder, it is all the more evident that those of ordinary skill in the art would not have been motivated to try DCL for the treatment of urticaria, due to the above-discussed toxicity concerns.

In sum, Berkow and Villani when combined do not suggest the claimed method. Moreover, even if they did, that alleged suggestion must be read in light of contrary teachings such as those of adverse effects.[12] Finally, the Examiner has not demonstrated that the reference would provide the required expectation of success. (*See In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991)). For at least these reasons, Applicants respectfully submit that the Examiner's contentions are without merit, and thus request that the rejection of the claims be withdrawn.

B. The Rejection Under 35 U.S.C. §103 over Swinyard, Villani, and Brandes, Should Be Withdrawn

On pages 6-10 of the Office Action, the claims are rejected for as allegedly obvious over the excerpts from *Remington's Pharmaceutical Sciences* (1990) ("Swinyard (I) and (II)"), in view of Villani and Brandes *et al.*, *J. Natl. Cancer Institute*, 86(10): 770-775 (1994) ("Brandes"). In particular, it is alleged that the claims are obvious because: (1) Swinyard (II) discloses the use of H_1-antagonists in the treatment of urticaria, and also discloses azatadine maleate, which has a structure according to the Examiner similar to loratadine and DCL, as one of the antihistamines; (2) Swinyard (I) discloses that not all antihistamines cause problems with P450 enzyme metabolism, and thus selection of non-problematic antihistamine is

[12] Applicants will discuss unexpected results below, which rebut a *prima facie* case of obviousness even if there was one. (*In re Chupp*, 816 F.2d 643, 646 (Fed. Cir. 1987)).

an effective way to avoid the side effects; and (3) Villani discloses that DCL is an antihistamine with low CNS-related side effects. Applicants respectfully traverse this rejection.

Swinyard (II) discloses that certain antihistamines **may** be effective in treating urticaria and other diseases while some may **not be** effective. Thus, Applicants submit that Swinyard (II) does not disclose[13] or suggest that DCL can be used for any purpose. Again, Swinyard (II) cannot suggest the use of DCL for the treatment of urticaria since Swinyard (II) teaches that while "enormous number of clinical conditions for which antihistaminic drugs have been suggested" are known, these drugs "vary from ***effective*** to ***ineffective*** in these conditions." (Swinyard (II) at last paragraph (emphasis in original)). Swinyard (II) recognizes "the complex therapeutic problem that confronts the thoughtful physician in the selection of antihistamine."[14] *Id.* Swinyard (II) clearly teaches not only that generalizations cannot be made regarding a particular antihistaminic agent's efficacy in treating a particular disease, but also that in fact not all antihistamines work.[15] Therefore, Swinyard (II) would not have suggested that antihistamines in general, much less DCL, can be used for the treatment of urticaria.

In response, the Examiner alleges that Applicants' arguments are based on "a misreading and/or a misunderstanding of Swinyard (II)," pointing to the portion of Swinyard (II) where it purportedly discloses that "the majority of [antihistamines] are effective in" various disorders, the list of which includes urticaria. (Office Action,

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[13] The Examiner alleges that Applicants are asserting that "a reference in an obviousness rejection requires meeting the standard of an anticipatory reference." Office Action, page 8. However, Applicants respectfully point out that one of the criteria for assessing the obviousness is to determine whether the cited references "disclose or suggest" the claimed invention, and this statement was made in lieu of assessing whether the reference discloses the claimed invention. (*See Motorola, Inc. v. Interdigital Tech. Corp.*, 121 F.3d 1461, 1473 (Fed. Cir. 1997)). As discussed below, the cited reference also does not suggest the claimed invention.

[14] Again, Applicants remind the Examiner that his cited art refers to physicians as the ordinary skilled artisan.

[15] In this regard, Applicants respectfully invite the Examiner's attention to references in the records that show that urticaria does not always respond to antihistamine drugs. (*See, e.g.*, Parslew, **Exhibit 3**, Abstract). Further, some studies showed that certain antihistaminic agents actually cause skin reactions, rather than treating them. (*See* Michel, **Exhibit 2**, and McClintock, **Exhibit 4**). There references are flatly contrary to the Examiner's assertions and should be considered by the Examiner. (*See* MPEP, § 2143.01).

page 8). However, Applicants respectfully point out that it is indeed the Examiner who misread what Swinyard (II) discloses.

This is because, although the statement referred to by the Examiner is provided as a general "introduction" of what antihistamines can do, Swinyard (II), following the description of various antihistaminic agents' uses and side effects, concludes that "[t]hese brief observations call attention to the enormous number of clinical conditions for which antihistaminic drugs have been suggested," and that "[t]hey also point up the fact that these drugs vary from effective to ineffective in these conditions." (Swinyard (II), page 1124, right column (emphasis added)). Therefore, it continues, "[w]hen considering the multiplicity of available antihistamines, their numerous untoward reactions and their propensity to induce sedation of variable intensity, one can appreciate the complex therapeutic problem" that confronts the physicians.[16] (*Id.* (emphasis added)). Based on these statements, it is evident that the "take-home message" for those of ordinary skill in the art reading Swinyard (II) is that there is no reasonable expectation of successfully using any and all antihistamines against urticaria. (*See Dow Chemical, supra*). Indeed, it is nothing more than an invitation to experiment. (*See, e.g., Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1380 (Fed. Cir. 1986)).

Furthermore, the Examiner appears to suggest that Swinyard (II) would have provided the required motivation because it discloses azatadine maleate as one of the antihistaminic agents, and azatadine maleate has a structure similar to loratadine and DCL. (Office Action, page 6). But as Applicants repeatedly pointed out in their previous responses and brief on appeal, the disclosure of an antihistaminic compound structurally similar to DCL would not have motivated the use of DCL. This is because antihistaminic agents structurally similar to DCL (*e.g.*, loratadine, terfenadine, and astemizole) were thought to be associated with cardiac side effects, personality change, or tumor promotion. (*See, e.g., Goodman & Gilman's The Pharmacological Basis of Therapeutics*, 9th Ed. (1996) ("Goodman"), page 590, a copy of which was provided in Applicants' previous response;[17] *see also* Storms

[16] Further, Applicants remind the Examiner that he has admitted in the record that urticaria is a complicated disorder not treated by all antihistamines. (*See* Office Action dated November 18, 2004, page 6).

[17] The Examiner implies, referring a portion of Goodman, that no side effects are observed for terfenadine, astemizole and loratadine. (Office Action, page 8). However, a

Declaration, ¶ 12-17 and Exhibits E5 and E7 thereto). As a result, one of ordinary skill in the art would have in fact been taught away from the claimed invention. (*See* MPEP, § 2143.01).

In response, the Examiner again disregards the Storms Declaration as allegedly pertaining to FDA standards.[18] However, as discussed above, it is well-established that adverse effects and toxicities, of a drug candidate, or a method of treatment using such compound, is a factor to be considered in determining the (non)obviousness of a claimed invention. (*Zenitz*, 333 F.2d at 928 and *Sasajima*, 212 U.S.P.Q. at 103). In other words, the question in the current case is that whether those of ordinary skill in the art would have been motivated to use DCL for the treatment of urticaria as claimed. As declared by Dr. Storms, those of ordinary skill it the art would not have been motivated because the concerns regarding serious adverse effects would have outweighed any motivation whatsoever to use DCL for the treatment of relatively trivial discomfort such as urticaria.

Regarding Swinyard (I), Berkow and Villani, Applicants maintain that they add nothing to the substance of the rejection. As the Examiner notes, Swinyard (I) discloses that only certain H_2-antagonists cause cardiac side effects, and the problem can be negated by selecting the right H_2-antagonist. Applicants agree. But in view of the fact that other antihistamines structurally similar to DCL were thought to be associated with cardiac side effects, Applicants submit that those of ordinary skill in the art would not have been motivated to select DCL. In addition, since Villani merely discloses the crude antihistaminic activity of compounds it discloses, it does not even provide any suggestion that its compounds, much less DCL, can be used for the treatment of urticaria at the doses claimed irrespective of the potential toxicity issue. (*See* Storms Declaration, ¶ 6-9).

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close reading of Goodman would reveal that the side effects referred to by that portion relate to the side effects known to be associated with first-generation antihistamines, such as sedation. Terfenadine, astemizole and loratadine, all being members of second-generation antihistamines, are not expected to have sedation as a side effect. In fact, the absence of sedation and related side effects is what distinguishes second-generation antihistamines from the first. However, terfenadine, astemizole and loratadine were reported prior to and at the time of the claimed invention to be associated with other serious side effects, including cardio-toxicity and tumor growth promotion, as pointed out by Applicants.

[18] Therefore, the Examiner does not provide any factual or scientific evidence to counter the statements made in the Storms Declaration.

The Examiner disagrees with Applicants, contending that "side effects [are] only one of many [factors] (reduced cost, improved selectivity, reduced dosage, etc.)" considered in the selection of an optimal antihistaminic agent by those of ordinary skill in the art. (Office Action, page 10). However, while there are many factors involved in the selection as the Examiner suggests, the concerns regarding toxicity of using a drug in a treatment method by the clinicians of Villani and physicians of Swinyard (II), particularly for non-life-threatening disorder such as urticaria, would evidently take precedent among these factors. Furthermore, as the Examiner points out, Swinyard (I) teaches that problems associated with a particular antihistaminic agent may be negated by selecting other appropriate antihistaminic agents. This is all the more reason why those of ordinary skill in the art would not have arrived at Applicants' claimed method since it was taught or suggested that DCL shared the common adverse effects with structurally similar antihistamines, in view of the fact that many other antihistaminic agents structurally unrelated to DCL were available.

Moreover, the Examiner disregards the fact that Villani does not suggest that DCL can be used for the treatment of urticaria, much less that it can be used in the claimed method at the low dose claimed. Villani's disclosure of DCL as being useful for treating "allergic reactions," would not have suggested to those of ordinary skill in the art that DCL could be used for the treatment of urticaria, much less at the dose claimed. The Examiner does not provide any evidence or reasoning to the contrary.

For the foregoing reasons, Applicants respectfully submit that no *prima facie* case of obviousness has been established by Swinyard (I) and (II), Brandes[19] and Villani, and thus request that the rejection under 35 U.S.C. § 103 be withdrawn.

C. Villani Alone or in Combination with the Cited References Fails to Render the Claims Obvious

The Examiner refers to Villani as the primary reference but rejects the claims over Berkow and Swinyard in view of Villani. For avoidance of doubt, Applicants submit the claimed methods are non-obviousness over Villani alone as the primary reference or in combination with Berkow, Swinyard (I) and (II) or all combined.

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[19] As shown in Section D below, Brandes not only fails to remedy the deficiencies of Swinyard (I) and (II) and Villani but actually motivate one of ordinary skill away from DCL by implicating the parent drug in tumor promotion. (*See* Applicants' Response of May 18, 2005, page 8).

Although Villani discloses DCL and shows crude or basic antihistaminic activity, Villani does not suggest the use of DCL in a method for treating urticaria. Indeed, when Villani is combined with Berkow or Swinyard, it is clear that more than the mere knowledge that DCL has antihistaminic activity is required to render the claimed treatment of urticaria obvious since each reference, Berkow and Swinyard, clearly teach not all antihistamines can treat urticaria.

Moreover, Applicants again submit as they did in the interview that Villani when read as a whole does not fairly suggest treatment with DCL of any disease at 5 mg/day or below. In this regard, Villani teaches for oral administration that the active compounds disclosed therein can be used as:

(a) 1 mg to 1000 mg depending upon application (column 8, lines 42-44);

(b) 5 to 100 mg/day, preferably 10 to 20 mg/day (column 11, lines 29-33) in two to four divided doses;

(c) tablets of 100 mg or 500 mg (Example A, column 22); and

(d) capsules of 100 mg or 500 mg (Example B, column 22).

Applicants submit that even though specific diseases are not taught or suggested, a fair reading of this seemly contradictory disclosure is use of amounts well above 5 mg and closer to 20 to 100 mg per day regardless of disease. In other words, since (a) is a general broad range, (b) prefers 10 to 20 mg/day in two to four divided doses and (c) and (d) use tablets or capsules of 100 or 500 mg, the reference fairly suggests amounts greater than 5 mg/day. The Examiner's contention to the contrary, particularly the reference teaches the use of 1.25 mg/dosage is mere hindsight reconstruction. Thus, Villani does not provide the suggestion of the claimed method of treating urticaria with a dose of 5 mg/day or less, much less provide a reasonable expectation of success. (*See Dow Chemical, supra*).

Even assuming *arguendo* that Villani does make such a suggestion for the treatment of urticaria with a low dose, it must be read in light of the potential concerns for the toxicity -- cardiotoxicity and tumor promotion among others -- that existed for compounds of this class. *See* Storms Declaration and cited art. In sum, when Villani, Berkow and Swinyard are properly considered, it is clear that even a combination of these references does not render the claimed invention obvious. The rejection should then be withdrawn.

D. Sufficient Unexpected Results Have Been Shown to Rebut All § 103 Rejections

As discussed above, Applicants reiterate that the claims are not obvious because a *prima facie* case of obviousness has not been established by the references cited by the Examiner. Even assuming, *arguendo*, that a *prima facie* case of obviousness were established by any of the Examiner's rejections, the Examiner must consider the evidence in the record demonstrating that the claimed method has surprising or unexpected benefits. Such evidence was presented, for example, in Examples 4 and 5 of the specification. This evidence alone is sufficient to rebut any *prima facie* case of obviousness. (*See In re May*, 547 F.2d at 1092-3; and *In re Chupp*, 816 F.2d at 646). In particular, Example 4 shows that DCL is 5 to 7 fold less potent in promoting tumor growth than loratadine. (Specification, Example 4). Such was unexpected in that those of ordinary skill in the art would have expected DCL to share certain fundamental properties with loratadine. (*See* Storms Declaration, ¶14).

Applicants note that the Examiner questions the data provided in Example 4, alleging that "the error limits for the data [which allegedly should have been disclosed in the specification according to the Examiner]... is not irrelevant, because said data would tell the ordinary practitioner whether the difference in neoplasm promotion between DCL and loratadine is statistically significant or not." (Office Action, page 9). However, as well-settled, the data presented in the specification cannot be questioned absent "some indication either from data or from the prior art that [the disclosed] tests give unreliable results." (*In re Kollman*, 595 F.2d 48, 56 (C.C.P.A. 1979), attached hereto as **Exhibit 9** (reversing the Board's decision that a claimed invention was obvious based on its conclusion that it was unclear whether the data provided in the specification is "statistically significant")). Here, the Examiner fails to provide any indication, either from the data itself or from the prior art, that the test disclosed in Example 4 gives unreliable results. Quite to the contrary, Applicants respectfully point out that the test described in Example 4 indeed provides reliable results.

For the avoidance of any doubt, Applicants invite the Examiner's attention to the Tarantino Declaration, submitted herewith.[20] In his declaration, Dr. Tarantino

[20] Attorneys for Applicants point out that the Examiner refused to review the Tarantino Declaration during the interview. Instead, the Examiner invited the Attorneys to make it of record by submission herewith. Applicants are submitting the Declaration as it

concludes that he would have concluded, based on Applicants' data disclosed in Example 4, that DCL was a better drug candidate than loratadine because Example 4 shows that DCL is less immunotoxic than loratadine. (*See* Tarantino Declaration, ¶ 9-11). Furthermore, Dr. Tarantino points out that Brandes itself shows that the *in vitro* assay disclosed in Example 4 correlates well to the *in vivo* tumor promotion assay disclosed in Brandes. (*Id.*, paragraphs 12-17). Based on this, Dr. Tarantino states that it would have been reasonable to conclude, based upon the data disclosed in Example 4 and what was known about the assay at the time (*see, e.g.*, Brandes), that DCL is less potent in promoting tumor growth than loratadine. (*Id.*, paragraphs 16-17).

In view of this data of unexpected results, the claimed method is non-obvious and all § 103 rejections should be withdrawn.

Furthermore, Dr. Tarantino indicates that Brandes' disclosure that loratadine and astemizole were found to be the agents with the highest potency in promoting tumor growth would have suggested that "piperidine H_1 antagonists," as a class, are likely be more immunotoxic and potent in promoting tumor growth, as compared with other classes of antihistamines. (*Id.*, paragraph 19). This, along with the Storms Declaration, attests to the fact that DCL, which shares structural similarities with loratadine and astemizole, would have been expected to share common adverse effects with those antihistamines as well. Again, Applicants respectfully point out that those of ordinary skill in the art would not have been motivated to use DCL for the treatment of relatively minor discomfort such as urticaria.

For these additional reasons, Applicants respectfully submit that the claims are not obvious over any combination cited by the Examiner of Swinyard (I) and (II), Berkow, Villani and Brandes, and thus respectfully request that the rejection be withdrawn.

VII. Conclusion

Applicants respectfully submit that all of the pending claims are allowable, and request that rejections directed to the claims be withdrawn.

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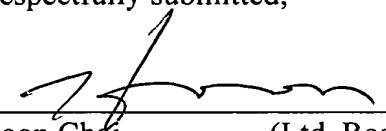
stood at the interview. The Examiner's shocking contention, in his Interview Summary, that Attorneys for Applicants made "what appeared to be disparaging remarks directed to the newly submitted complementary declaration" is simply incorrect.

No additional fee is believed due for this submission. Should any additional fees be due for this submission or to avoid abandonment of the application, please charge such fees to Jones Day Deposit Account No. 503013.

Respectfully submitted,

Date January 9, 2006



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Attachments